AMENDMENT TRANSMITTAL LETTER

AMENDMENT TRANSMITTAL LETTER Applicant(s): Molly F. Kulesz-Martin			Attorney Docket No: RPP:135D US
Serial No: 08/644,289	Filing Date: May 10, 1996	Examiner: Y. Eyler	Art Unit: 1642
Invention: p53as PROTEIN AND ANTIBODY THEREFOR			

TO THE COMMISSIONER OF PATENTS AND TRADEMARKS:

Transmitted herewith is an amendment in the above-identified application. The fee has been calculated as shown below:

CLAIMS AS AMENDED					
	CLAIMS REMAINING AFTER AMEND.	HIGHEST NUMBER PREV. PAID FOR	NUMBER EXTRA CLAIMS PRESENT	RATE	ADDITIONAL FEE
TOTAL CLAIMS	17 -	20 =	0	X $18	$ 0
INDEP. CLAIMS	6 -	6 =	0	X $78	$ 0
TOTAL ADDITIONAL FEE FOR THIS AMENDMENT					$ 0

[X] No additional fee is required.

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Respectfully submitted,

Dated: November 8, 1999

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PATENT
RPP:135D US

11-27-99

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Molly F. Kulesz-Martin	Art Unit:	1642
Serial No:	08/644,289		
Filed:	May 10, 1996		
Examiner:	Eyler, Y.		
For:	p53as PROTEIN AND ANTIBODY THEREFOR		

I certify that this **RESPONSE** is being deposited on **November 8, 1999,** with the U.S. Postal Service as first class mail addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231

Michael L. Dunn
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RESPONSE

The Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is in reply to the Official Action of August 4, 1999.

In the above Official Action, the Examiner has made many rejections based upon 35 U.S.C. 112 many of which revolve around the differences between p53 and p53as.

The Examiner is making the invention much more complicated than it is. The invention is easy to understand and can be practiced to the extent of the breadth of the claims by one of even meager skill in the art in view of the teachings of the specification.

The Examiner should be reminded that a patent specification is not intended to be a textbook including all information known and readily available to a skilled person. If such were

not the case, every patent specification would be thousands of pages long rehashing known material ad nausem and hiding the nature of the improvement of the invention within unnecessarily included information.

The present invention is not difficult to understand in view of the specification and claims. One skilled in the art already knows a myriad of effects of p53. One skilled in the art already knows that p53 has growth regulating properties discussed in literally hundreds of documents. One skilled in the art already knows that p53 has a terminal negative regulatory domain that can turn off many, if not all, of the growth regulating properties of p53 under certain conditions. One skilled in the art already knows that when the negative regulatory domain is removed, the growth regulating properties of p53 can no longer be turned off.

The Examiner is referred to the 58 references cited in the information disclosure statement as examples of such known information and is especially referred to Hupp et al. cited by the Applicant that shows that removal of the C-terminal regulatory domain permanently activates p53. ***This paper was accepted for publication in the prestigious technical journal "Cell" in 1992 after peer review. Neither the reviewers nor the magazine had any difficulty understanding the meaning of "active" p53 or the "function".*** **Since those skilled in the art understand the meaning of these terms, any objection by the Examiner to their use should be dropped**.

The present invention points out that in view of the above, one would further expect that the growth regulating properties of p53 also could no longer be turned off if the terminal regulatory domain of p53 were modified or substituted to interfere with its function and

demonstrated that to be the case by the discovery of terminally modified p53 that cannot be turned off (p53as) and that has a terminal sequence that raises a unique antibody.

One skilled in the art knows the sequence of p53. One skilled in the art knows many epitopes that can raise unique antibodies. One skilled in the art already knows how to truncate p53 to remove the negative regulatory domain and one skilled in the art already knows how to connect different sequences.

Therefore, in view of her above discovery of terminally modified p53 that cannot be turned off (p53) having a terminal sequence that raises a unique antibody, the inventor concluded that p53 could be easily truncated to remove the negative regulatory domain and a large number of different terminal sequences could be substituted that raise unique antibodies. The probability that such a new terminal sequence would also have a negative regulatory domain effect upon p53 is infinitesimal. In view of her discovery and teaching it becomes clear that known methodologies may be combined to practice the invention and that it would be surprising if the p53as having unique terminal sequences did not function as active p53 and it would be further surprising if the p53as having unique terminal sequences did not raise the expected unique antibodies.

Further, if there are any p53 terminated sequences, as above described, that do not function as active p53 and that do not produce unique antibody, such could easily be detected in view of existing knowledge.

All of the rejections under 35 U.S.C. 112 related to function of p53 and p53as and the differences between p53 and p53as, are therefore being argued as a group and all of them

should be withdrawn for the reasons given above. Nobody of even meager skill in the art would fail to understand the scope the present claims. Further, anybody of even meager skill in the art would be able to practice the invention in view of the specification.

The citation of the Harris et al. reference in a 35 U.S.C. 112 rejection is inappropriate but in any case ***anything said by Harris et al. is irrelevant to any valid rejection since it was published about six months after the filing date of the present application.***

The Examiner has rejected Claims 16 and 19 under 35 U.S.C. 112 on the ground that the metes and bounds of "portion of the peptide SEQ ID NO:1" is indefinite on the ground that "portion" cannot be determined. The sequence has only 20 amino acids. One skilled in the art can easily, with little effort, test subsequences within that 20 amino acid sequence to determine if an antibody is raised to the subsequence. Such determinations are routinely made by technicians and college undergraduates. This routine test may be easily made for any subsequence, if one skilled in the art desires to know if it is within Claims 16 and 19. There is no ambiguity and no indefinitness.

The Examiner has rejected Claims 1, 3-6, 8-11, and 17 on the ground that they contain subject matter not described in the specification at the time the application was filed. The Applicants disagree. The specification clearly teaches modification of the C terminus as admitted by the Examiner. Further the specification teaches that certain terminally modified p53's (p53as's) raise unique antibodies. Since the only difference between the p53's and p53as's is in the terminal sequence, it is clear from the disclosure that the antibodies are raised to the unique terminal portions. One skilled in the art knows that the only way to raise a unique

antibody is to have a unique active epitope. This teaching clearly indicates to one skilled in the art that other terminal modifications (taught) can also have unique epitopes. The rejection should be withdrawn.

The Examiner has rejected Claims 1, 3-6, 8-11, 17, and 18 under 35 U.S.C. 112 as containing new matter.

This rejection seems to be similar to, if not identical with, the rejection described above. With due respect to the Examiner, it is clearly taught that the terminal sequence of p53 must be eliminated or modified to eliminate the negative regulatory domain to obtain consistent activity and the discovery of the wild type p53as having a modified terminal sequences is evidence thereof, especially when taken in conjunction with the existing knowledge in the art that elimination of the terminal sequence also creates a continuously active p53 (See Hupp et al.) The limitation of consistent functionality between active p53 and p53as is completely proper as function of p53 is clearly described in the existing art. The Examiner continues to be moved by the fact that usually substitution within a protein sequence to obtain similar function is complex. ***The Examiner would normally be correct but is not correct here.*** The functional sequences in p53 and p53as have been identified, are the same and are not being changed. ***Only the terminal regulatory domain is being affected by the changes to obtain the claimed p53as***. The total elimination of the regulatory domain in the known art while retaining p53 activity is dispositive of whether or not function may be retained while modifying that domain.

The Examiner is again referred to page 3, lines 6-7 of the specification which says: "To obtain a p53as the terminal amino acids of p53 are preferably modified, i.e., there is at least

some substitution, as opposed to simple truncation." Further, beginning at the bottom of page 8 it is stated: "Further evidence for specificity of the p53as antibody is reactivity of anti-p53as with p53as but not with the major p53 protein." Details of antibody specificity for p53as and not for p53 are then given in several subsequent paragraphs. Since the modifications illustrated in the specification are at the C terminus, the claims have been limited to that embodiment, i.e. p53 and p53as are defined as being sequentially identical up to the final 50 carboxy terminal amino acids of p53. The teaching with respect to the specific p53as is clearly an example of terminally modified p53 having a unique epitope. The teaching is not limiting.

It is thus clearly taught in the specification that modification of the terminal amino acids of p53 can be used to eliminate the regulatory domain. Nothing further is required to enable one skilled in the art to do it The advantages of a unique C terminus epitope are also clearly taught. Again, at the present state of the art, any genetic engineering lab technician could add such a unique epitope to the C terminus.

A patent application is not supposed to be a textbook in well understood procedures. The teachings have been made of how to eliminate the negative regulatory domain of p53 by removing or altering the carboxy terminal sequence. Once this teaching is made, one of even menial skill in the art can do it Further, the desirability of incorporating a unique epitope is taught in the specification. Again, once this teaching is made, one of even menial skill in the art can do it. It is the concepts, taught in the present application, of eliminating the negative regulatory domain and incorporating a unique epitope which is at the heart of the invention. Once these concepts are taught, one having only minimal skill can practice them since only well

known standard procedures are needed. Certainly no undue experimentation is required or necessary.

In view of the above and other teachings in the specification, one skilled in the art would clearly know that other epitopes could be substituted in the C terminus. The claims have thus been appropriately limited to the minimum difference between p53 and p53as defined on page 2, last paragraph without addition of new matter.

The rejection should be withdrawn.

Claims 16 and 19 have been rejected under 35 U.S.C. on the ground that use of "any portion of SEQ ID NO:1" is not enabled. As previously discussed, SEQ ID NO:1 is a short sequence and anybody with even minimal skill in the art would be enabled to easily determine whether a portion of that sequence raised an antibody. Undue experimentation would not be required as the test is practically "cookbook". The rejection should be withdrawn.

Claims 1, 3-5, 8-11, 17 and 18 have been rejected under 35 U.S.C. 102(b) as being anticipated by Wolf et al. or Arai et al.

Claim 6 has been rejected under 35 U.S.C. 103 over Wolf et al. and Arai et al. above in view of Lee et al.

The attorney for the Applicants does not understand why these rejections are being maintained. Prior responses have already pointed out significant differences between this cited art and the claimed invention yet the Examiner continues to attribute teachings to the cited references that are simply not there.

The present invention requires that p53as be the same as p53 up to the carboxy terminal group. By contrast, M-8 has the cyst residue of p53 at amino acid 132 replaced by a phe residue. A corresponding RNA or cDNA must have corresponding nucleic acid changes. M-8 further has a large 96 base pair ***embedded (not terminal)*** nucleic acid chain (and corresponding predicted amino acid) insert at nucleic acid 1092. These are not changes in the terminal sequence but internal changes that apparently completely alter the function and nature of the protein as previously described. Yet the Examiner continues to assert that p53 and M-8 sequences are the same when they are not. Some of the glaring differences in function are given in the prior two responses and the Examiner is urged to look at them.

Any rejection relying upon M-8 against p53as is thus improper under both 35 U.S.C. 102 and 103. The rejections based upon Wolf et al. or Arai et al. should therefore be withdrawn.

The addition of Lee et al to the other cited references accomplishes nothing. Lee et al. is generic and says nothing concerning p53 or p53as. Further, as previously discussed, neither Wolf et al. nor Arai et al. disclose or suggest a p53as, as defined in the claims, anyplace in the entire universe and certainly not in a plasmid or virus. Lee et al. does not cure this glaring defect of the Wolf et al. and Arai et al. references.

The Examiner has again rejected Claims 1, 3, 4, and 17 under 35 U.S.C. 103 over Han et al. and again it is asserted that the rejection is improper and should be withdrawn.

Han et al. is interested in sequencing p53as cDNA and for that purpose only incorporates a p53as cDNA segment into a plasmid. The incorporated segment is only about one-third of a complete p53as cDNA. A whole p53as cDNA is never incorporated into a plasmid and in fact

would be counterproductive for Han et al.'s purposes. Large DNA fragments are difficult and sometimes impossible to sequence thus Han et al actually teaches against incorporating an entire p53as cDNA sequence.

Han et al. does not incorporate p53as cDNA or any other functional p53 or p53as into anything.

In the present Official Action, the Examiner has acknowledged that Han et al. does not incorporate p53as into anything but based entirely upon hindsight asserts that because Han et al. inserts a p53as segment, it would be obvious to insert the whole p53as just because Han et al. says "more precise biochemical and biological characterizations of AS-p53 protein ... appear to be critical in future studies of p53 function...." Attributing the teaching of incorporation of a complete p53as into a plasmid or virus based upon the above quoted statement Han et al. is impermissible hindsight at a minimum.

This conclusion of the Examiner is contrary to the teaching of Han et al. which is to sequence the segment. In general it is not desirable to try to sequence large segments; thus, following the teachings of Han et al. there is no reason to incorporate the entire p53as. The Examiner's extension of Han et al. to the entire p53as is classical hindsight. In the absence of the teaching of the present application, there would simply be no reason to incorporate the entire p53as into a vector of any kind.

Combining Han et al. with Sambrook et al. accomplishes nothing (and is a new ground of rejection). It is a giant reach to state that because Sambrook et al. generically discloses expressing large amounts of protein with nothing at all suggested concerning p53as, Han et al.

somehow suggests incorporating a whole p53as. This is a clear impermissible hindsight combination. Further, a generic teaching of expressing a large amount of protein is not equivalent to saying that long sequences can or should be incorporated into plasmids. Large amounts of protein and long sequences are not the same thing or even similar. One has essentially nothing to do with the other.

The rejection of Claims 5, 6, 8-11 and 18 over Han et al. in view of Lee et al. is a similarly flawed hindsight combination.

Han et al. does not teach or suggest incorporation of p53as into anything, as previously discussed, and the Examiner's assertion to the contrary is overreaching and classical hindsight. Citation of Lee et al. which discloses nothing at all concerning p53as, does not cure this defect. Neither reference suggests incorporating p53as into anything; therefore their combination certainly makes no such suggestion.

The rejection should be withdrawn.

In summary, none of the references cited by the Examiner in any of the rejections suggest incorporating p53as into anything. None of the cited references cure this critical defect in any of the other references. Any assertion to the contrary requires giant leaps of logic based upon the applicants own disclosure and is classical hindsight despite the Examiners unsupported assertions to the contrary.

All rejections should be withdrawn and all claims should be allowed which action is courteously requested.

Respectfully submitted,

Dated: November 8, 1999

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